REMARKS

Claims 42 and 46 are currently pending in the present application. Claims 42-50 were subject to a restriction requirement, and claims 42-44 and 46-47 were elected in a Response filed June 4, 2001. Also in that Response, claims 43, 44, and 47 were canceled. Claims 45 and 48-50 were withdrawn from consideration by the Examiner as being drawn to a non-elected invention.

Rejection of Priority Status

The Examiner has rejected the priority claim to U.S. patent application no. 08/025,408, filed February 26, 1993. Applicants respectfully disagree with the Examiner's assertion that the claims of the present application are not supported by the parent application.

Applicants point out that claim 1 of the parent application is directed to a method of removing antigens from a patient with an autoimmune disease or AIDS by passing a fluid drawn from the patient through an immunosorbent, which consists of antibodies to at least one interferon (gamma or alpha interferon), and one or more antibodies to tumor necrosis factor. Thus, Applicants argue that the priority document discloses use of antibodies to gamma interferon, antibodies to alpha interferon, and antibodies to tumor necrosis factor (TNF) to remove these cytokines from a patient. Thus, the basic knowledge that removal of gamma and alpha interferons and TNF from the blood of a patient suffering from an autoimmune disease or AIDS is beneficial in relieving the symptoms associated with AIDS is taught in the parent application. For this reason, Applicants respectfully request that priority to U.S. Patent Application No. 08/025,408 be granted.

Preliminary Amendment "A" filed January 20, 2000

Applicants note that the Examiner has not entered "most of the amendments" in Preliminary Amendment "A" due to quantity and apparent ambiguousness of location where the specification should be amended. Preliminarily, Applicants note the Examiner has incorrectly indicated that the Amendment was made pursuant to 37 CFR §1.312. This section applies to amendments after allowance only.

Additionally, Applicants respectfully point out to the Examiner that this identical Preliminary Amendment was entered in full for an application related to the present application, U.S. Application No. 08/995,730, now issued U.S. Patent No. 6,333,032 B1. Applicants do not

understand why the Office entered the Amendment for the related application, but has refused to enter the Amendment for the present application, which has an identical specification as U.S. Patent No. 6,333,032 B1. Applicants request that the Amendment be entered here.

In the event that the Examiner refuses entry of the amendments, Applicants respectfully request that the Examiner indicate which amendments were entered, and request that the Examiner provide instructions as to how the remainder of the amendments can be entered.

References Not Considered

The Examiner indicated that the IDS references AF, AR, BT, CD, and CN were not considered because the Office apparently never received said references. All references were submitted with the Information Disclosure Statement filed in parent application no. 08/771,831, now issued U.S. Patent No. 5,888,511. However, as a courtesy to the Examiner, Applicants enclose herewith a copy of the above-listed references for the Examiner's consideration.

Rejection of claims 42 and 46 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 42 and 46 for reciting the term "antibody to tumor necrosis." As suggested by the Examiner, Applicants have amended the claims to recite the word "factor" following said phrase, thereby rendering the rejection moot.

Claim 46 was also rejected for reciting the term "including," since, in the Examiner's view, it is not clear what entities other than those specifically listed are encompassed by the claim. As suggested by the Examiner, claim 46 has been amended to recite the term "or" in place of the term "including," thereby rendering the rejection moot.

Applicants respectfully request that the rejection of the claims under 35 U.S.C. §112 second paragraph be reconsidered and withdrawn.

Rejection of claims 42 and 46 under 35 U.S.C. §112, first paragraph, enablement

The Examiner has rejected claims 42 and 46 as lacking enablement. Specifically, the Examiner has contended that the specification is only enabling when using antibodies against TNF-alpha. In the Examiner's view, antibodies to other TNF molecules have not been enabled. In the interest of expediting prosecution, Applicants have amended claim 42 to recite antibodies to TNF-alpha, thereby rendering the rejection moot. As to this rejection, Applicants respectfully request that the Examiner please reconsider and withdraw the rejection.

The Examiner has also rejected the claims as lacking enablement for functional

equivalents and derivatives of antibodies useful in the invention. Applicants respectfully traverse this rejection.

In the Examiner's view, the specification does not enable one of skill in the art to make or use the invention as it is claimed because the scope of the terms "derivative" and "functional equivalent" is too broad. Applicants point out the that the terms objected to are defined on page 21, lines 4-14 of the instant specification and submit that these terms are familiar to those skilled in the art.

The basic premise of antibody technology, which is well known in the art, is that an antibody binds with a part of an antigen and the antibody-antigen complex is removed from a patient's system. The same basic premise applies here. A combination of antibodies is circulated through a patient, which antibodies bind with their respective antigens during circulation. The antibody-antigen complex is then removed from the patient's system. Antibody technology is well-known in the art, and would dictate that a skilled artisan could develop, quite easily, antibodies having added moieties or antibody fragments which would bind the same antigens as the complete antibody. One of skill in the art could then easily test whether these derivatives and/or functional equivalents bind the antigens in the same or substantially similar manner as the antibodies described in the present invention. Developing these functional equivalents and derivatives and performing the tests to determine the binding capacity of these functional equivalents and derivatives do not require undue experimentation. In fact, this kind of testing is routine in art of antibody technology, for example, in preparing pharmaceutical compositions that are more tolerable by a patient.

Routine experimentation, even if it is quantitatively overwhelming, is not undue if all the knowledge to perform such experiments is before the artisan. In the landmark enablement case of *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^{8} M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where the art typically engages in a complex, but routine degree of experimentation, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*. Even assuming, *arguendo*, that developing and testing various derivatives and functional equivalents is considered to be complex experimentation, Applicants submit that this kind of experimentation, while complex, is routine in the art, and therefore, is not undue experimentation.

For all of the foregoing reasons, Applicants respectfully request that the Examiner reconsider and withdraw the rejection to the claims.

Rejection of claims 42 and 46 under 35 U.S.C. §112, first paragraph, written description

The Examiner has rejected claims 46 and 49 as containing subject matter which was not described in the specification. Preliminarily, Applicants note that claim 49 has been withdrawn from consideration, and Applicants assume that the Examiner intended to reject claims 42 and 46. Working under that assumption, Applicants respectfully traverse this rejection.

In the Examiner's view, the specification does not adequately disclose the scope

of a "functional equivalent" or a "derivative." Applicants point out that both of these terms are defined on page 21, lines 4-14 of the instant specification. Applicants assert that these terms are known in the art and adequately described in the present specification. Functional equivalents of the antibodies disclosed in the invention are those equivalents that bind to the same antigenic determinant as the disclosed antibodies. Thus, one of skill in the art would know that in order for a functional equivalent to bind to the same antigenic determinant, the antibody binding site would have to be similar at least in sequence and/or structure to the antibodies taught in the invention, otherwise the functional equivalent would not bind with the antigenic determinant. In addition, one of skill in the art would also know what types of molecules would serve as functional equivalents. For example, a single-chain antibody having the same antigenic determinant as the antibodies taught in the invention would be encompassed as a functional equivalent. Likewise, an antibody having the same antigenic determinant but a different variable region would also be an example of a functional equivalent.

Further, the term "derivative" is defined in the specification as including functional and chemical derivatives of an antibody, including fragments, segments, variants, and analogs thereof. A chemical derivative contains moieties that are normally not present on the molecule. Such chemical derivations include acetylation, thiolation, methylation, and glycosylation, for example. While the specification does not define a functional derivative, one skilled in the art would know that a functional derivative is one which performs the same or substantially similar function as the antibodies of the present invention, but which does not necessarily have the same form or structure. The level of skill in the relevant art is high, and those skilled would know which derivatives would work in the present invention.

As discussed above, the basic premise of antibody technology applies here, where a combination of antibodies is circulated through a patient and bind with their respective antigens during circulation. The antibody-antigen complex is then removed from the patient's system. Antibody technology is well-known in the art, and would dictate that a skilled artisan could develop, quite easily, antibodies having added moieties or antibody fragments which would bind the same antigens. Thus, Applicants respectfully submit that since the level of skill in the art is high and antibody technology is so widely used, a written description fraught with methods of derivitizing an antibody and methods of creating antibody fragments from a given antibody would be redundant and unnecessary, as it is not required to reiterate that which is already well-

known in the art.

Thus Applicants put forth that there is sufficient written description to support the scope of "functional equivalents" and "derivatives" and respectfully request that the Examiner withdraw the written description rejection.

Rejection of claims 42 and 46 under 35 U.S.C. §103(a)

The Examiner has rejected claims 42 and 46 as being obvious in view of the combination of three prior art references, Uehara (1993, J. Interferon Res. 13S1:PW6-9), Probert (1995, PNAS 92:11294-11298), and Skurkovich (U.S. Patent No. 4,824,432). Preliminarily, Applicants point out that should the priority date of the parent application be granted in light of the foregoing arguments, Uehara and Probert are not prior art with respect to the original priority date of the application.

However, even in the event that the Examiner does not award the February 26, 1993 priority date to the present application, Applicants submit that the combination of Uehara, Probert, and Skurkovich does not render the present invention obvious.

In order for a combination of references to render an invention prima facie obvious, three factors must be met. First, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references, when combined) must teach or suggest all the claim limitations. MPEP §2143. These factors have not been met by the Examiner's arguments.

The Examiner argues that since each of the references teaches use of one of the antibodies of the combination taught in the present invention, combining the references to arrive at the present invention would have been the logical progression of a skilled person having seen each of the antibodies individually in the prior art. Applicants respectfully disagree and note that this is not the proper test for obviousness.

There is no suggestion in any of the references to combine the teachings of the other cited references to arrive at the present invention. Applicants point out that the Probert reference is not even related to immune-related symptoms of AIDS. Rather, Probert deals with CNS-related symptoms of AIDS and how to relieve such symptoms. Probert does not discuss

that immune-related symptoms of AIDS can be relieved by removing antibodies to TNF-alpha.

In addition, there is no suggestion in Skurkovich to combine it with either Probert or Uehara since Skurkovich does not suggest that removing TNF might be therapeutically beneficial to an AIDS patient. Indeed, Skurkovich teaches only that removal of alpha interferon is therapeutic to an AIDS patient. Similarly, the Uehara abstract makes a statement that the symptoms of the murine analog to AIDS are delayed when mice are treated with antibody to gamma interferon. Uehara does not teach or suggest that administration of any other antibody in combination with antibody to gamma interferon would be more beneficial to treat AIDS.

Further, none of the references indicates that by combining the antibody taught in a particular with another antibody taught in one of the cited references will be reasonably successful in achieving a therapeutic result which is better than using each antibody individually. There were no data in any of the references demonstrating that combining antibodies to gamma and alpha interferon and antibody to TNF was therapeutically more beneficial than using each antibody individually. Moreover, one skilled in the art would not have been motivated to combine these references since no data were provided that would indicate a therapeutic benefit to using the antibodies in combination.

In addition, Applicants also point out that since no evidence is indicated that would lead one skilled in the art to believe that a combination of antibodies would be more beneficial than administering antibodies individually, one skilled in the art would know the possibility exists that administering combination antibody therapy may have an opposite effect, thereby being a therapeutic detriment. It is quite possible that in administering combination therapy, the antibodies might have had some inhibitory effects on each other, or the combination may have had some negative effect on the patient. As we now know, this is not the case. But it is the present application that presents data for the first time that indicates the positive therapeutic effect of combination antibody therapy. Therefore, there can be no reasonable expectation of success that a therapeutic benefit would be conferred if the antibodies were administered in combination.

Finally, since each of the references teaches only one antibody, none of the references can overcome any of the shortcomings of the other references. Thus, combining just two of the references in any combination, will not render the present invention obvious.

Applicants contend that the Examiner has not met the burden of proving a prima

facie obviousness case. For the foregoing reasons, Applicants respectfully request that the rejection of the claims under §103(a) be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has either been overcome or is now inapplicable, and that each of the claims 42 and 46 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

SIMON SKURKOVICH, *ET AL.*

February 27, 2002 By: _____
(Date)

KATHRYN DOYLE, Ph.D., J.D.
Registration No. 36,317
MORGAN, LEWIS & BOCKIUS, L.L.P.
1701 Market Street
Philadelphia, PA 19103-2921
Telephone No.: 215-963-5000
Direct Telephone: 215-963-4723
Facsimile: 215-963-5299
E-Mail: kdoyle@morganlewis.com

KD/GHL

Marked up Copy of Amended Claims

42. (Twice Amended) A method of treating Acquired Immunodeficiency Disease in a patient comprising administering to said patient an effective amount of a combination of an antibody to gamma interferon, an antibody to alpha interferon, and an antibody to tumor necrosis factor-alpha.

46. (Amended) The method of claim [33] 42, wherein said antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, and combinations thereof, [including] or biologically active fragments, functional equivalents, derivatives, or allelic or species variants thereof.